Amendments to Specification

Please amend the title on page 1 at lines 1-2 in the following manner:

AROMATIC SULFONE **HYDROXAMIC ACIDS** ~~**HYDROXAMATES**~~ AND THEIR USE AS PROTEASE INHIBITORS

Please amend Paragraph 1 in the following manner:

[1] This patent claims priority **as a divisional of U.S. Patent Application Serial No. 10/142,737 (filed May 10, 2002), which, in turn, claims priority** to U.S. Provisional Patent Application Serial No. 60/290,375 (filed May 11, 2001). The entire text of **each of the above-referenced applications** ~~**U.S. Provisional Patent Application Serial No. 60/290,375**~~ is incorporated by reference into this patent.

Please amend Paragraph 2 in the following manner:

[2] This invention is directed generally to proteinase (also known as "protease") inhibitors, and, more particularly, to aromatic sulfone ~~**hydroxamates (also known as "aromatic sulfone**~~ hydroxamic acids **["] (including hydroxamates)** that, *inter alia,* inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to compositions of such inhibitors, intermediates for the syntheses of such inhibitors, methods for making such inhibitors, and methods for preventing or treating conditions associated with MMP activity and/or aggrecanase activity, particularly pathological conditions.

Please amend Paragraph 14 in the following manner:

[14] A wide variety of **hydroxamic acid** ~~**hydroxamate**~~ compounds also have been reported to inhibit MMPs. Such compounds reportedly include **hydroxamic acids** ~~**hydroxamates**~~ having a carbon backbone. *See, e.g.,* WIPO Int'l Pub. No. *WO* 95/29892. *See also*, WIPO Int'l Pub. No. WO 97/24117. *See also*, WIPO Int'l Pub. No. WO 97/49679. *See also*, European Patent No. EP 0 780 386. Such compounds also reportedly include **hydroxamic**

acids ~~**hydroxamates**~~ having peptidyl backbones or peptidomimetic backbones. *See, e.g*, WIPO Int'l Pub. No. WO 90/05719. *See also*, WIPO Int'l Pub. No. WO 93/20047. *See also*, WIPO Int'l Pub. No. WO 95/09841. *See also*, WIPO Int'l Pub. No. WO 96/06074. *See also*, Schwartz et al., Progr. *Med. Chem.*, 29:271-334(1992). *See also*, Rasmussen et al., *PharmacoL Ther.*, 75(l): 69-75 (1997). *See also*, Denis et al., *Invest New Drugs*, 15(3): 175-185 (1997). Various piperazinylsulfonylmethyl **hydroxamic acids** ~~**hydroxamates**~~ and piperidinylsulfonylmethyl **hydroxamic acids** ~~**hydroxamates**~~ have additionally been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 00/46221. And various aromatic sulfone **hydroxamic acids** ~~**hydroxamates**~~ have been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 99/25687. *See also*, WIPO Int'l Pub. No. WO 00/50396. *See also*, WIPO Int'l Pub. No. WO 00/69821.

Please amend Paragraph 16 in the following manner:

[16] Many known MMP inhibitors exhibit the same or similar inhibitory effects against each of the MMPs. For example, batimastat (a peptidomimetic **hydroxamic acid** ~~**hydroxamate**~~) has been reported to exhibit IC_{50} values of from about 1 to about 20 nM against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat (another peptidomimetic **hydroxamic acid** ~~**hydroxamate**~~) has been reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum similar to batimastat, except that Marimastat reportedly exhibited an IC_{50} value against MMP-3 of 230 nM. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(l): 69-75 (1997).

Please amend Paragraph 20 in the following manner:

[20] Various **hydroxamic acid** ~~**hydroxamate**~~ compounds have been reported to inhibit aggrecanase-1. Such compounds include, for example, those described in European Patent Application Publ. No. EP 1 081 137 A1. Such compounds also include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/09000. Such compounds further include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/59874.

Please amend Paragraph 21 in the following manner:

[21] In view of the importance of **hydroxamic acid** ~~**hydroxamate**~~ compounds in the prevention or treatment of several pathological conditions and the lack of enzyme specificity exhibited by two of the more potent MMP-inhibitor drugs that have been in clinical trials, there continues to be a need for **hydroxamic acids** ~~**hydroxamates**~~ having greater enzyme specificity (preferably toward MMP-2, MMP-9, MMP- 13, and/or aggrecanase (particularly toward MMP-13 in some instances, toward both MMP-2 and MMP-9 in other instances, and aggrecanase in yet other instances), while exhibiting little or no inhibition of MMP-1 and/or MMP-14. The following disclosure describes **hydroxamic acid** ~~**hydroxamate**~~ compounds that tend to exhibit such desirable activities.

Please amend Paragraph 22 in the following manner:

[22] This invention is directed to **hydroxamic acid** ~~**hydroxamate**~~ compounds (and salts thereof) that inhibit pathological protease activity (particularly compounds that inhibit MMP-2, MMP-9, MMP- 13, and/or aggrecanase activity), while generally exhibiting relatively little or no inhibition against MMP-1 and MMP-14 activity. This invention also is directed to a method for inhibiting MMP activity and/or aggrecanase activity, particularly pathological MMP and/or aggrecanase activity. Such a method is particularly suitable to be used with mammals, such as humans, other primates (*e.g.*, monkeys, chimpanzees. etc.), companion animals (*e.g.*, dogs, cats, horses. etc.), farm animals (*e.g.*, goats, sheep, pigs, cattle, etc.), laboratory animals (*e.g.*, mice, rats, etc.), and wild and zoo animals (*e.g.*, wolves, bears, deer, etc.).

Please amend Paragraph 55 in the following manner:

[55] In accordance with this invention, it has been found that certain aromatic sulfone **hydroxamic acids** ~~**hydroxamates**~~ tend to be effective for inhibiting MMPs, particularly those associated with excessive (or otherwise pathological) breakdown of connective tissue. Specifically, Applicants have found that these **hydroxamic acids** ~~**hydroxamates**~~ tend to be effective for inhibiting proteases (particularly MMP-2, MMP-9, MMP- 13, other MMP's associated with pathological conditions, and/or aggrecanase) that are often particularly

destructive to tissue if present or generated in abnormally excessive quantities or concentrations. Moreover, Applicants have discovered that these **hydroxamic acids** ~~**hydroxamates**~~ tend to be selective toward inhibiting pathological protease activity, while avoiding excessive inhibition of other proteases (particularly MMP-1 and/or MMP-14) that are typically essential to normal bodily function *(e.g.,* tissue turnover and repair).

Please amend Paragraph 686 in the following manner:

[686] The **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an inhibitory activity against MMP-1 or MMP-14 that is substantially less than its inhibitory activity against MMP-2, MMP-9, or MMP-13. In other words, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an in inhibition constant (K_i) against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its inhibition constant(s) against at least one of MMP-1 and MMP-14. The inhibition constant of a compound or salt thereof may be determined using an *in vitro* inhibition assay, such as the K_i assay described below in Examples 55-89.

Please amend Paragraph 687 in the following manner:

[687] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

Please amend Paragraph 688 in the following manner:

[688] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

Please amend Paragraph 689 in the following manner:

[689] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Please amend Paragraph 690 in the following manner:

[690] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Please amend Paragraph 691 in the following manner:

[691] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Please amend Paragraph 692 in the following manner:

[692] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

Please amend Paragraph 693 in the following manner:

[693] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

Please amend Paragraph 694 in the following manner:

[694] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Please amend Paragraph 695 in the following manner:

[695] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed

that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Please amend Paragraph 696 in the following manner:

[696] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Please amend Paragraph 697 in the following manner:

[697] The activity and selectivity of a **hydroxamic acid** ~~**hydroxamate**~~ compound or salt may alternatively be determined using an *in vitro* IC_{50} assay, such as the IC_{50} assay described below in Examples 55-89. In that instance, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its IC_{50} value(s) against at least one of MMP-1 and MMP-14.

Please amend Paragraph 698 in the following manner:

[698] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

Please amend Paragraph 699 in the following manner:

[699] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

Please amend Paragraph 700 in the following manner:

[700] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Please amend Paragraph 701 in the following manner:

[701] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Please amend Paragraph 702 in the following manner:

[702] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably

no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Please amend Paragraph 703 in the following manner:

[703] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

Please amend Paragraph 704 in the following manner:

[704] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

Please amend Paragraph 705 in the following manner:

[705] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

Please amend Paragraph 706 in the following manner:

[706] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

Please amend Paragraph 707 in the following manner:

[707] In some particularly preferred embodiments, the **hydroxamic acid** ~~**hydroxamate**~~ compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-**1**3 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

Please amend Paragraph 726 in the following manner:

[726] A wide variety of methods may be used alone or in combination to administer the **hydroxamic acids** ~~**hydroxamates**~~ and salt thereof described above. For example, the **hydroxamic acids** ~~**hydroxamates**~~ or salts thereof may be administered orally, parenterally, by inhalation spray, rectally, or topically.

Please amend Paragraph 727 in the following manner:

[727] Typically, a compound (or pharmaceutically acceptable salt thereof) described in this patent is administered in an amount effective to inhibit a target MMP(s). The target MMP is/are typically MMP-2, MMP-9, and/or MMP-13, with MMP-13 often being a particularly

preferred target. The preferred total daily dose of the **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof (administered in single or divided doses) is typically from about 0.001 to about 100 mg/kg, more preferably from about 0.001 to about 30 mg/kg, and even more preferably from about 0.01 to about 10 mg/kg (*i.e.*, mg **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

Please amend Paragraph 728 in the following manner:

[728] Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and condition of the patient; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof employed; whether a drug delivery system is utilized; and whether the **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and, therefore, can deviate from the preferred dosage regimen set forth above.

Please amend Paragraph 729 in the following manner:

[729] This invention also is directed to pharmaceutical compositions comprising a **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof described above, and to methods for making pharmaceutical compositions (or medicaments) comprising a **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof described above.

Please amend Paragraph 731 in the following manner:

[731] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the **hydroxamic acids** ~~**hydroxamates**~~ or salts thereof are ordinarily combined with one or more adjuvants. If administered *per os*, the

hydroxamic acids ~~**hydroxamates**~~ or salts thereof can be mixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in a dispersion of the **hydroxamic acid** ~~**hydroxamate**~~ or salt thereof in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

Please amend Paragraph 734 in the following manner:

[734] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The **hydroxamic acids** ~~**hydroxamates**~~ or salts thereof can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, com oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers.

Please amend Paragraph 883 in the following manner:

[883] **Part C.** The product from **Part B** (530 mg, 0.91 mmol) was dissolved in 4N HC1 in dioxane (5 mL) and methanol (1 mL). After 15 min at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 360 mg of the desired **hydroxamic acid** ~~**hydroxamate**~~. Purification by reverse phase HPLC afforded 270 mg (59%) of the title compound. ESMS m/z = 504 $[M+H]^+$. HRMS calculated for $C_{25}H_{28}N_2O_7S$: 501 . 1695 $[M+H]^+$, found: 501. 1689.

Please amend Paragraph 1050 in the following manner:

[1050] Several **hydroxamic acids** ~~**hydroxamates**~~ and salts thereof were analyzed in *in vitro* assays to determine their ability to inhibit the MMP cleavage of peptide substrates. Inhibition (K_i) and IC_{50} constants were calculated from the assayed ~~**hydroxamate**~~ **hydroxamic acid**-MMP interactions.

Please amend Paragraph 1059 in the following manner:

[1059] The stock solutions of the assayed **hydroxamic acids** ~~**hydroxamates**~~ (or salts thereof) were prepared in 1% dimethyl sulfoxide (DMSO). These stock solutions were diluted in Buffer A (100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, 0.05% polyoxyethylene 23 lauryl ether, pH 7.5) to obtain solutions with different **hydroxamic acid** ~~**hydroxamate**~~ concentrations, *i.e.*, assay solutions with different concentrations of the assayed MMP inhibitory compound. The experiment controls contained the same amount of Buffer A/DMSO as the assayed sample, but contained no **hydroxamic acid** ~~**hydroxamate**~~ (or salt thereof).

Please amend Paragraph 1060 in the following manner:

[1060] The assays from which the IC_{50} determinations were made were performed as follows. The MMPs were activated with either trypsin or APMA (4-aminophenylmercuric acetate, Sigma Chemical, St. Louis, MO). The assayed **hydroxamic acid** ~~**hydroxamate**~~ samples were incubated in Microfluor™ White Plates (Dynatech, Chantilly, VA) and analyzed on a Perkin Elmer L550 plate reader (Norwalk, CT). The excitation wavelength was 328 nm, and the emission wavelength – 415 nm. All samples (assayed **hydroxamic acids** ~~**hydroxamates**~~ and controls) were incubated in separate plates at room temperature in the presence of 4 μM of MMP substrate (I). As stated in the previous paragraph, samples containing varying concentrations of the same assayed **hydroxamic acid** ~~**hydroxamate**~~ were prepared. Inhibition was measured as a reduction in fluorescent intensity as a function of MMP inhibitor concentration.

Please amend Paragraph 1061 in the following manner:

[1061] The assays from which the K_i determinations were made were performed as follows. The assayed **hydroxamic acid** ~~**hydroxamate**~~ samples were incubated in separate wells of untreated white polystyrene plates (Nunc Nalgene International, Rochester, NY), and analyzed on a Tecan SpectraFlour Plus plate reader. The excitation wavelength was 330 nm, and the emission wavelength – 420 nm. All samples (assayed **hydroxamic acids** ~~**hydroxamates**~~ and controls) were incubated in separate plate wells at room temperature for 1 hr in the presence of 4 μM of MMP substrate (II). In the absence of MMP inhibitory activity, substrate II was cleaved at the Gly-Leu bond resulting in an increase of relative fluorescence. Inhibition was observed as a reduced rate of this increase in relative fluorescence. The various **hydroxamic acids** ~~**hydroxamates**~~ were analyzed using a single low enzyme concentration with a single substrate concentration fixed at or below the K_m. This protocol is a modification of method by Knight et al., *FEBS Lett.*, 296(3), 263-266 (1992). Apparent inhibitory constants were determined by non-linear regression of reaction velocity as a function of inhibitor and enzyme concentration using Morrison's equation, as described by Kuzmic, Anal. Biochem. 286, 45-50 (2000). Modifications were made in the non-linear regression method to allow a common control reaction rate and effective enzyme concentration to be shared between all dose-response relationships on a given assay plate. Since the substrate concentration was chosen to be at or below the K_m, the apparent K_i's from this analysis were reported as K_i's without correction for the influence of substrate.

Please amend Paragraph 1114 in the following manner:

[1114] Additional **hydroxamic acid** ~~**hydroxamate**~~ compounds (and salts thereof) can be prepared by one skilled in the art using methods similar to those described in **Examples 1-54** alone or in combination with techniques well known in the art. Such compounds include, for example, the compounds summarized in the following **Table 7**. **Table 7** also summarizes *in vitro* MMP inhibition results obtained by Applicants with the listed **hydroxamic acids** ~~**hydroxamates**~~. As with **Table 5**, all *in vitro* K_i and IC_{50} results in **Table 7** are given in nM units. The Ki measurements are in parenthesis.

Please amend the abstract on page 634 in the following manner:

This invention is directed to aromatic sulfone ~~hydroxamates (also known as "aromatic sulfone~~ hydroxamic acids **["]** **(including hydroxamates)** and salts thereof that, *inter alia,* inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to a prevention or treatment method that comprises administering such a compound or salt in an MMP-inhibiting and/or aggrecanase-inhibiting effective amount to an animal, particularly a mammal having (or disposed to having) a pathological condition associated with MMP and/or aggrecanase activity.